

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re application of:

LAZAR et al.

Serial No. 10/672,280

Filed: September 26, 2003

For: *OPTIMIZED Fc VARIANTS
AND METHODS FOR THEIR
GENERATION*

Examiner: Chun Wu Dahle

Group No. 1644 Confirmation No.: 8317

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Signed: 

Ada O. Wong

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR REHEARING UNDER 37 CFR § 41.52

This Request for Rehearing (“Request”) is being submitted in response to the Decision on Appeal mailed on March 17, 2011 (“Decision”). This is being filed on or before May 17, 2011 within two months of the Decision, making it a timely request. In the Decision, the BPAI (“the Board”) affirmed the rejection of Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142, and 144 as obvious over Presta¹ and summarily affirmed double patenting over a number of applications due to the affirmation of the Presta rejection. Appellants respectfully request reconsideration of the Decision as regards the two affirmed rejections.

¹ U.S. 6,737,056 B1, issued May 18, 2004 to Presta

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ARGUMENT

I. The Board Overlooked the Fact that It Previously Held that Presta Did Not Teach Particular Individual Substitutions at Stated Position

Applicability of Watkins

On page 7, lines 8-16, the Decision states that as Watkins related to a different position (280) and involved a 102(b) rejection, it is not applicable here. The Decision overlooked the fact that Presta² serves as the basis of the prior art rejection in both *Ex parte* Watkins (Appeal 2007-2523, decided 9/12/2007) and the instant case; that Watkin's 102 determination and the instant 103 determination, while different in nature, are both premised on an assessment of the prior art teachings; that both 280 and 239 were recited in Presta's Claim 13; and that an assessment of Presta's teachings, including Claim 13, has already been made in Watkins. The points overlooked were stated on pg. 24, lines 9-10, pg. 25 of the Appeal Brief and pg. 5, lines 3-14 of the Decision. The response is that Watkin's determination of what Presta teaches is binding on the Board according to principles of *stare decisis*. Appellants would like to direct the Board's attention to *In re Tanaka*,³ a Federal Circuit case decided on the basis that principles of *stare decisis* govern Board decisions alike. Since positions 239 and 280 are both recited in Presta's Claim 13 and both the Board in this Decision and in Watkins based their decision on Presta's teachings, the Watkins decision is relevant here.

Specific Teaching of Presta

² U.S. Patent No. 6,737,056 (issued May 18, 2004), referred herein as Presta.

³ *In re Tanaka* (Appeal No. 2010-1262) decided 4/15/11 by the Federal Circuit. As outlined in 37 CFR 41.52(f)(2), Appellant can rely on recent case law.

On page 10, lines 15-18, the Decision states that “Presta teaches that one can make substitutions at position 239, and that those substitutions may be with one of the 20 ... naturally occurring amino acids.” The Decision overlooked the fact that the Board has previously decided on the teachings of this identical reference, stating that “we do not agree that Presta provides a specific teaching of substituting the amino acid at position 280 with each of these twenty amino acids.”⁴ The point overlooked was made to the Board on pg. 25, lines 1-21 of the Appeal Brief. The response is that the Board cannot “fly counter to principle of *stare decisis*”⁵ by discounting the Board’s previous findings in Watkins, which held that Presta does not teach any of the 20 standard amino acid substitutions at a given position. Position 280 is listed along position 239 in Claim 13, as one of 59 different positions and since it is Presta’s teachings that are relied upon by the Board for its Decision, the findings in Watkins are relevant to the present inquiry. As such, Presta does not teach 239DEQT by virtue of listing 59 different positions, one or more of which could be subject to amino acid modifications. The only 239 variant Presta discloses is S239A and it demonstrates reduced binding to FcγRII and FcγRIIIA. Thus, Presta does not teach any specific 239 variant including 239T.

II. The Board Overlooked the “Teachings of the Reference As a Whole”

Selection of Position 239 from a List of 59 Positions

On page 9, lines 11-13, the Decision states that “it would have been obvious to substitute the serine at position 239 with other naturally occurring amino acids.”

⁴ Ex parte Jeffry D. Watkins and Barrett Allan, Appeal 2007-2523, pg. 6

⁵ See pg. 5, lines 21-23 of *In re Tanaka*.

The Decision misapprehended Presta's Claim 13, which recites a polypeptide comprising "an amino acid modification" not just at position 239, but at any one or more of a list of 59 amino acid position including 239. The point misapprehended was first made in the opinion of the Board on page 5, lines 3-14. The response is that the claimed genus in Presta is not a mere set of 19 amino acid changes as the Board presupposes. Firstly, the Decision misconstrued the term "amino acid modification" to mean a substitution with one of 20 naturally occurring amino acids. Such an interpretation runs contrary to the explicit definition set forth in Presta and the specific holding in *Watson*, where the Board stated that Presta contemplates both naturally occurring and non-naturally occurring amino acids. Secondly, the Decision overlooked the total teachings of Claim 13, which recite a 59 positions; to arbitrarily select position 239 from this list utilizes impermissible "hindsight reconstruction", as specifically rejected by the Supreme Court in KSR⁶.

Presta Reference Teaches Away from Position 239

On page 9, lines 9-14, the Decision states that Presta "specifically claims a variant at position 239 that has increased binding to a FcγR" and "that it would have been obvious to substitute the serine at position 239 with other naturally occurring amino acids and screen for the desired activity with a reasonable expectation of success of obtaining variants with increased binding to a FcγR." The Decision overlooked the 5 references in Presta associating 239 variants with **reduced** binding to FcγR since none of these points were addressed in the

⁶ KSR Int'l. Co. v. Teleflex Inc. (2007) 550 U.S. 398 at 421.

Decision. The Decision also overlooked the point that the sole disclosure associating 239 with increased binding to FcγR should be weighted, given its reliance on post-filing amendments. The points overlooked were made to the Board on pg. 26, lines 11-24 and pg. 27, lines 1-23 of the Appeal Brief. The response is that the Board unduly relied on the single citation in Presta associating position 239 with increased binding to FcγR, i.e. Claim 13⁷, without accounting for contrary teachings associating 239 variants with reduced binding to FcγR.⁸

An obviousness determination rests on a comparison of the claimed invention with the reference as a whole.⁹ Pursuant to MPEP 2141.02(V1), “(a) prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.” Without taking into account the multiple contrary teachings in Presta, the Board did not appreciate what the reference as a whole apprised an ordinary artisan. Having failed to reconcile the contrary teachings in Presta with the single statement¹⁰ of increased binding property of a 239 Fc variant, the Board could not have reached an informed opinion of what Presta teaches as a whole. The Board based its decision on an incomplete set of facts, from which contrary teachings were excluded¹¹.

III. The Board Overlooked the Selection of a “Lead Compound”

⁷ See FF11, pg. 5, lines 3-14 of the Decision.

⁸ See pgs. 26-27 in their entireties and pg. 29, lines 10-11 of the Appeal Brief.

⁹ See pg. 11, l. 16-pg. 12, l. 28 & pg. 13, ll. 3-10 of the 1/14/2009 Resp to OA.

¹⁰ Claim 13 of Presta.

¹¹ See para. 1, pg. 26 and para. 2, pg. 29 of the 2/16/2010 Appeal Brief.

On page 9, lines 8-10, the Decision states that the Presta patent “specifically claims a variant at position 239 that has increased binding to an FcγR”. The Decision overlooked that claim 13 recites 59 different positions, not just 239, and thus ignores the 58 other positions in its hindsight-guided selection of 239 as a “lead compound”. The point overlooked was made in the Opinion of the Board on 5, FF11. The response is that Presta teaches an enormous breadth encompassed by 59 recited positions and a broad range of amino acid modifications possible at these 59 positions, with no motivation to select 239 as a position for modification other than Appellants’ own claim. The Board is reminded herein of the Federal Circuit’s admonishment against “hindsight reconstruction.”¹² Presta does not provide any reason for selecting 239DEQT. In fact, an ordinary artisan would be disinclined to elect a position 239 variant, amongst the many possibilities, for increased binding affinity to FcγR when Presta demonstrates S239A’s decreased binding to all 4 tested FcγRs¹³ and the disclosure as a whole associates 239 variants with reduced binding. Ensuing from this misreading of Claim 13 was the Board’s denial of *Takeda*’s¹⁴ relevance to the Appeal.¹⁵ Now that the scope and content of Claim 13 are accurately drawn, Appellants shall present the similarities between *Takeda* and the instant Appeal once more. Rather than a finite number of identified, predictable solutions, the prior art in both *Takeda* and the instant Appeal:

¹² See pg. 14 of Daiichi.

¹³ See pg. 30, line 20-pg. 31, line 2 of the Appeal Brief.

¹⁴ *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007).

¹⁵ See pg. 9, lines 18-21 of the Decision.

disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound ... exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious it was “obvious to try.” The evidence showed that it was not obvious to try. See pg. 1, lines 6-16 of the Appeal Brief.

On page 8, lines 19-22, the Decision states that “Presta ... teaches that threonine is the preferred substitution for serine (FF9). Thus, it would have been obvious to the ordinary artisan to substitute threonine for serine at position 239 (the claimed 239T substitution).” A conservative substitution of wt residue Ser would at best be expected to give wild-type activity and, thus, no increased activity. The Decision misapprehends the standard by which obviousness is established and mistakes structural similarity for obviousness. The point is best illustrated in a decision, *Daiichi v. Matrix* (Fed. Cir. Case no. 2009-1511), rendered after Appellants’ submission of the Appeal Brief on 2/16/ 2010. The response is that obviousness is not some inference that can be drawn simply from an observed structural similarity between a prior art compound and the claimed compound.

Proof of obviousness based on structural similarity requires clear and convincing evidence that a medicinal chemist of ordinary skill would have been motivated to select and then to modify a prior art compound (e.g., a lead compound) to arrive at a claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old. See pg. 11, lines 14-21 of Daiichi.

In *Daiichi*, the Federal Circuit found no motivation exists in selecting and modifying the prior art compound, ‘902 Example 6, to arrive at a claimed compound even when the prior art compound differed from the patented compound by only a single oxygen atom at one position. Here, the single Presta variant (239A) which must be selected as the lead to make additional changes differs from the claimed 239DEQT compounds by much more than is present in *Daiichi*. For example, the amino acid change A→D replaces H with a carboxylic acid moiety, A→E replaces H with CH₂COO⁻, A→Q replaces H with CH₂C(O)NH₂) and A→T replaces H with a hydroxy group and another H with a methyl group. The rationale in *Daiichi* was that “a medicinal chemist of ordinary skill would not have been motivated to select the ‘902 compounds over other second-generation ARBs... because many of the latter ARBs demonstrated greater potency,”¹⁶ ranging from 7 to 180 times the potency of the closest prior art compound. The Federal Circuit held that “it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds”¹⁷ and that “proving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds.”¹⁸ The data associated with this “lead”, S239A, is reduced binding to **all four FcγR**

¹⁶ See pg. 13, lines 14-34 of *Daiichi*.

¹⁷ See pg. 14, lines 21-24 of *Daiichi*.

¹⁸ See pg. 14, lines 21-34 of *Daiichi*, which further explains that “the attribution of a compound as a lead compound after the fact must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention.”

receptors. There is no motivation for the chemist in search of better FcγR binding to select position 239 as a lead out of all the choices available in Presta given its poor data. The Decision overlooks the abundance of other Fc variants with favorable binding activity in Presta, ranging from 1.01-2.06 times the wild-type.¹⁹ Even taking Claim 13 into account, there is no reason to select 239 over the many alternatives taught and demonstrated in Presta to possess superior binding affinity. Given the many parallels between *Daiichi* and the instant case, Appellants believe the Federal Circuit decision should dictate the outcome of the present Appeal.

IV. The Board Overlooked That Obviousness Cannot be Predicated On the Unknown

On page 8, beginning in line 24, the Decision states that “(t)he S239T variant would inherently have the property of increased binding affinity to an FcγR.” The point was first made in the Decision. The response is that per *Watkins*, there is no specific teaching of S239T, and thus there can be no inherency. The Federal Circuit has stated that “obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established.”²⁰ “To be inherent, the claimed limitation must ‘necessarily flow’ from the teachings of the cited reference.”²¹ Per *Watkins*,²² Presta does not teach the claimed variants 239DEQT. Likewise, these variants’ increased binding affinity to a FcγR were unknown at the time of the invention. The functional

¹⁹ See Tables 6-8 of Presta. The difference is not simply one of degree; >1 indicates increased binding and < 1 indicates reduced binding.

²⁰ See *In re Rijckaert*, 9 F.2d 1531 (Fed. Cir. 1993) and MPEP 2141.02.

²¹ See pg. 12, lines 9-17 of the Resp to Office Action filed October 30, 2007.

²² See pg. 18, line 26-pg. 19, line 7 of Response to 8/4/2008 OA.

limitation at issue, therefore, could not be said to “necessarily flow” from something the reference does not teach. As such, the present claims directed to 239DEQT, with increased binding affinity to an FcγR are not obvious over Presta on the basis of inherency. In addition, the present claims are directed to a species, which is patentable over a disclosed genus.²³ A claimed genus does not bar patentability of any and all species encompassed therein.

V. The Board Overlooked the Lack of Predictability of Amino Acid Substitutions Based on Activity

On page 9, lines 9-14, the Decision states that “it would have been obvious to substitute the serine at position 239 with other naturally occurring amino acids and screen for the desired activity with a reasonable expectation of success of obtaining variants with increased binding to a FcγR.” The Decision overlooked data in Presta specifically showing significant variation in activity, and thus unexpectedness, associated with different amino acid substitutions. The points overlooked were made to the Board on pg. 31, line 13-pg. 32, line 8. The response is that the Presta reference demonstrates the unpredictability of amino acid substitutions by showing that different amino acid substitutions at the same position render dramatically different results. This in turn supports a finding of unexpectedness and thus non-obviousness.²⁴

²³ See pg. 8, lines 25-26 and pg. 9, lines 17-18 and 24 of the Resp to Office Action filed January 14, 2009 and pg. 40, lines 13-16 of the Appeal Brief.

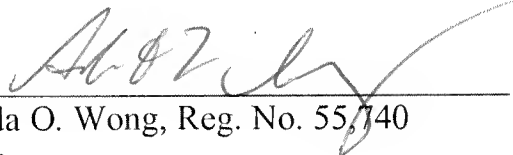
²⁴ See data for position 267, 269 and 318 in Tables 6-8 as well as a number of additional examples in Presta illustrating the unpredictability of making amino acid changes.

Authorization is granted to charge any outstanding fees due at this time for the continued prosecution of this matter to Morgan, Lewis & Bockius LLP Deposit Account No. 50-0310 (Client-Matter No. 067461-5121-US). In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 CFR 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0310, order no. 067461-5121-US.

Respectfully submitted,

MORGAN LEWIS & BOCKIUS LLP

Date: 5/17/11
Customer No. **67374**
MORGAN, LEWIS & BOCKIUS LLP
One Market, Spear Street Tower
San Francisco, CA 94105
Telephone: 415.442.1000
Facsimile: 415.442.1001
awong@morganlewis.com


Ada O. Wong, Reg. No. 55,740
for
Robin M. Silva, Reg. No. 38,304
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